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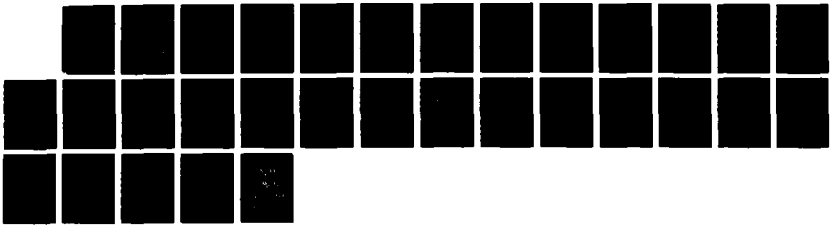

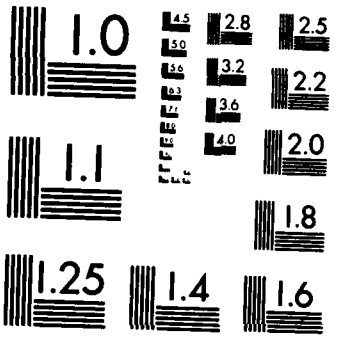

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USE OF MODERATELY HYPERTONIC SODIUM CHLORIDE IN THE RESUSCITATION OF PATIENTS FROM INJURY

ANNUAL/FINAL REPORT

APRIL 1, 1987

JAMES W. HOLCROFT, M.D.
MARY J. VASSAR, R.N.

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DAMD17-85-C-5096

University of California
Davis, California 95616

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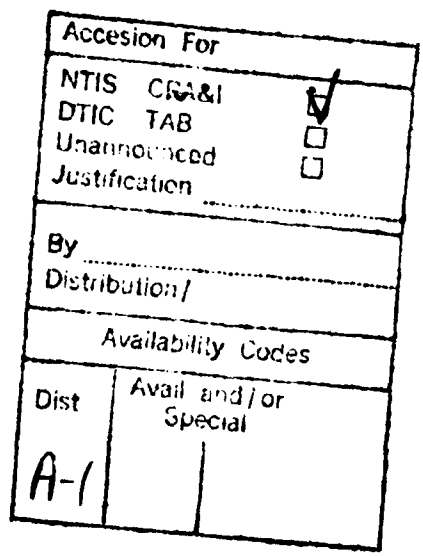

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Hypertonic sodium chloride; moderately hypertonic solutions; trauma, fluid resuscitation; systolic blood pressure; heart rate; urine output; P_aO_2/F_iO_2 ratio; fluid administered; patients; survival; shock; trauma; isotonic solutions; lactated Ringer's; organ failure; 3% sodium chloride; blood replacement; pulmonary function; crystalloid solutions.

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The purpose of this contract was to test the hypothesis that 3% sodium chloride will 1) successfully resuscitate hemodynamically unstable patients who have been subjected to major trauma; and 2) will achieve this resuscitation with infusion of smaller volumes of solution than required by patients resuscitated with standard isotonic solutions. Based on the promising work with hypertonic solutions in animal models of shock, this study was begun as a means of obtaining clinical experience in patients undergoing operative repair of traumatic injuries. Over 3 hours, ten severely

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injured patients received 3% sodium chloride, 4 ml/kg/hr, in addition to isotonic fluids as needed to maintain urine output and blood pressure. Ten patients served as controls and received isotonic fluids only. At the end of 2 hours, the cumulative fluid requirements in the 3% sodium chloride group were 39±17 ml/kg versus 69±35 ml/kg ($p<0.03$) in the patients treated with standard isotonic solutions. The 3% sodium chloride patients had significant improvements in urine output and more rapid correction of acidosis. Pulmonary function, as measured by P_aO_2/F_iO_2 indices, remained stable throughout the first 24 hours in the 3% NaCl group. The P_aO_2/F_iO_2 indices deteriorated significantly in the isotonic treatment group. There were no adverse effects associated with the 3% sodium chloride treatment. The results from this trial are very promising and should now allow us to initiate trials evaluating the efficacy of more concentrated sodium chloride solutions earlier in the course of injury, where they are expected to be of the most benefit.

SUMMARY

One of the main causes of death following traumatic injury has been hemorrhagic shock. Based on numerous studies in animal models and in burn shock patients, there has been considerable interest in evaluating the efficacy of hypertonic sodium chloride solutions in the resuscitation for traumatic injury. The purpose of this contract was to initiate the clinical evaluation of a 3% sodium chloride (3% NaCl) solution versus resuscitation with standard isotonic solutions.

Twenty hemodynamically unstable trauma patients were entered into the study. Each patient had received at least 15 $ml \cdot kg^{-1}$ of isotonic solutions in the hour before entry. All patients had received at least 6 liters of crystalloid and 2 units of blood since their injury. Studies were initiated within the first six hours after injury. Ten patients then received 3% NaCl, 4 $ml \cdot kg^{-1} \cdot hr^{-1}$, in addition to isotonic fluids as needed to maintain urine output and blood pressure. Ten patients served as controls and received isotonic fluids only. By the end of two hours the volume of crystalloid replacement in the 3% NaCl group was 44% less than the volume of fluid required by the isotonic group. Systolic blood pressures remained equivalent. In addition, there was significant improvement in urine output and more rapid correction of metabolic acidosis in the patients treated with 3% NaCl. Pulmonary function, as measured by PaO_2/FiO_2 indices, remained stable throughout the first 24 hours in the 3% NaCl group. The PaO_2/FiO_2 indices deteriorated significantly in the isotonic treatment group. These beneficial effects in the clinical setting support the experimental models that demonstrate superiorities of small volumes of hypertonic solutions in resuscitation from shock.

FOREWORD

For the protection of human subjects, the investigator(s) have adhered to policies of applicable Federal Law 45CFR46.

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BODY OF REPORT

Background

Early adequate fluid resuscitation remains crucial to the ultimate survival of the hypovolemic injured solider. The majority of deaths from trauma occur prior to or in the first few hours after reaching a treatment facility, and are due to either rapid hemorrhage or central nervous system trauma (1). Infusion of standard isotonic solutions frequently requires the administration of several liters of fluid in order to maintain hemodynamic stability. In the field setting, it is impossible for medical personnel to administer such large volumes of fluid (2). Hypertonic sodium chloride (NaCl) solutions have been used extensively in the resuscitation of patients from burn shock (3,4,5). In this clinical setting, they have been shown to decrease the total water load required for adequate resuscitation, a factor which may prove valuable in the ultimate survival of the patient.

Shackford and colleagues studied the effects of infusing moderately hypertonic (514 mOsm) sodium lactate solution to 30 patients udergoing elective abdominal aortic reconstruction (6). Twenty-eight patients in the lactated Ringer's group received 10 liters of fluid for intra-operative maintenance of cardiovascular stability; the hypertonic group required 5 liters.

Extremely hypertonic solutions have been used to resuscitate dogs, sheep, rats, and pigs from hypovolemic shock (7,8,9,10,11,12). These solutions achieve excellent cardiovascular resuscitation and do so with infusion of very small quantities of fluid. In addition, in dogs and pigs, hypertonic solutions improve survival rates when compared to infusion of equivalent volumes of normal saline (12,13).

Resuscitation with small volumes of hypertonic NaCl offers many potential advantages for the care of injured soldiers and civilians. Besides the immediate improvements in hemodynamics and survival shown in the animal studies, a medic could potentially treat and stabilize a larger number of soldiers for transport to base hospitals. Hypertonic sodium chloride may attenuate cerebral edema in those who have suffered head injuries (14,15,16).

The purpose of this contract was to test the hypothesis that 3% sodium chloride (1028 mOsm) will: 1) successfully resuscitate hemodynamically unstable patients (as defined in methods) who have been subjected to major trauma; and 2) achieve this resuscitation with infusion of smaller volumes of solution than required by patients resuscitated with standard isotonic solutions.

The specific objectives of this contract were to:

1. Assess the volume of 3% sodium chloride necessary to achieve adequate resuscitation.

2. Assess adequacy of shock resuscitation with 3% sodium chloride, including assessment of correction of metabolic acidosis, assessment of oxygen delivery, and assessment of oxygen consumption.

3. Assess the cardiovascular response to 3% sodium chloride, including assessment of systemic arterial pressure, cardiac index, and filling pressures of the heart.

4. Assess the pulmonary response to 3% sodium chloride, including the need for support of ventilation and oxygenation.

5. Assess the renal response to 3% sodium chloride, including urine output and including excretion of sodium, chloride, creatinine, solute, and free water.

6. Assess the hepatic response to 3% sodium chloride.

7. Assess the neurological response to 3% sodium chloride.

8. Assess the influence of 3% sodium chloride resuscitation on 30 day mortality.

Methods

Criteria for Entry

Patients were entered into the study if they:

1. Were 18 years of age or older; and

2. Were subjected to major trauma in the previous 6 hours; and

3. Had evidence of hemodynamic instability:

   a. Requiring at least 6 liters of crystalloid solution since the time of injury; and

   b. Were known to have hypotension at any time with a mean systemic arterial pressure less than 70 mmHg.

4. Had received at least 2 units of blood replacement; and

5. Had received 15 $ml \cdot kg^{-1}$ of crystalloid during the previous hour and were expected to continue receiving at least 15 ml/kg of fluid over the next hour (as indicated by the anesthesiologist or surgeon).

Patients were excluded if:

1. Their admission serum creatinine was greater than 2.0 mg/dl.

2. Their admission serum sodium concentration was greater than 147 mEq/L.

3. Their admission serum sodium concentration was less than 130 mEq/L.

4. Their serum chloride concentration was greater than 105 mEq/L.

5. Their admission serum potassium concentration was less than 3.5 mEq/L.

6. Their calculated serum osmolality was greater than 295 milliosmols/kg.

7. They had a history of a seizure disorder.

8. The had a history of cirrhosis.

9. They had a history of congestive heart failure.

10. They were more than 6 hours from the time of injury.

Resuscitation Protocol

Patients were randomized into a 3% NaCl or lactated Ringer's treatment group according to who the attending surgeon was at operation. Patients in the 3% NaCl group were given 4 $ml \cdot kg^{-1} \cdot hr^{-1}$ of solution for up to 3 hours. Patients in the lactated Ringer's group received 12 $ml \cdot kg^{-1} \cdot hr^{-1}$ of solutions. Additional isotonic fluids were infused as needed at the discretion of the anesthesiologist or the surgeon using standard clinical judgement for maintenance of adequate urine output and blood pressure. Figure 1 illustrates the algorithm for infusion of NaCl or lactated Ringer's solution.

It should be mentioned that the volumes of the 3% NaCl and lactated Ringer's group were selected largely out of clinical practicality. All patients were going to receive at least 15 $ml \cdot kg \cdot hr^{-1}$ of fluid at the time of entry. We believed that the most prudent protocol would be one which did not interfere with ongoing resuscitation efforts. To administer only 4 $ml \cdot kg \cdot hr^{-1}$ of 3% NaCl and 4 ml.kg.hr-1 of lactated Ringer's would not have been practical. Thus, the 4 ml.kg.hr-1 of 3% NaCl was essentially a supplement to the large volumes of isotonic fluid being administered at the time of entry.

Measurements

Serum samples were collected for measurement of chemistry panels, blood counts and blood gases, which were performed in the hospital laboratories. Vital signs, ventilator settings, and strict measurements of fluid intake and output were collected by the clinical research nurse throughout the infusion protocol. Subsequent measurements were collected from the operating room, and nursing flow sheets. Injury severity scores were calculated, utilizing standard criteria (17,18).

The incidence of mortality and the presence or absence of organ failure at any time during the 30 days after entry into the study was evaluated. Severe organ failure was defined as follows:

Respiratory failure: requirment for mechanical ventilation with a ratio of systemic arterial partial pressure of oxygen to inspired oxygen concentration (P_aO_2/F_iO_2) less than 150 mmHg for a period of more than 24 hours after

admission to the intensive care unit or the need for more than 3 days of mechanical ventilation. **Cardiac failure:** A cardiac index less than 3.0 liters·minutes^{-1}·meter^{-2} with a pulmonary arterial wedge pressure greater than 20 mmHg. **Hepatic failure:** one or more serum bilirubin concentrations greater than 5.0 mg/dl in the absence of hemolysis. **Renal failure:** one or more creatinine concentrations greater than 3.0 mg/dl. **Gastrointestinal failure:** any upper gastrointestinal hemorrhage requiring transfusion. **Intravascular coagulation:** a platelet count less than 50,000 cells/mcl with fibrin monomers and fibrin degradation products present in the serum on one or more occasions.

Statistics

The study was to be terminated if either 100 patients were entered or when a difference in net volume administered to the two groups was demonstrated at the 5% level or less. All data are reported as means ± 1 standard deviation. When measurements were not available in all patients, the number of patients in whom the measurement was made is indicated by the letter N. All probabilities were calculated using a two-tailed student's unpaired t-test. Mortality was evaluated with Fisher's Exact Test.

Results

Characteristics of Patients at Time of Entry

Between July 1985 and April 1986, 1,156 patients were admitted to the trauma service. There were 579 operations and 131 deaths. Twenty severely injured patients were entered into the study -- 10 in the 3% NaCl and 10 in the lactated Ringer's group. Approximately 35 patients were excluded: 10 had been stabilized by the time the research nurse had reached the operating room; 10 more were more than 6 hours from their injury; 5 had electrolyte abnormalities; 10 lacked central venous catheters (which were initially required at the early phase of the study).

The mechanism of the injury for patients entered into the study is indicated in Tables I and II. Five patients in the 3% NaCl group and 4 patients in the lactated Ringer's group suffered blunt injuries. Five of the 3% NaCl patients and six of the lactated Ringer's patients suffered penetrating injury. Tables III and IV show that the baseline vital signs, laboratory values, urine output, fluid and blood replacement were similar for the two groups, with the exception of the P_aO_2/F_iO_2 ratios and platelet counts. The patients in the 3% NaCl group had a mean P_aO_2/F_iO_2 ratio of 240 ± 131 versus 380 ± 135 in the lacated Ringer's group ($p<0.03$). The platelet counts for the 3% NaCl group were 231,000 ± 17,000 (cells/mcl) versus 149,000 ± 77,000 for the lactated Ringer's group ($p<0.03$). The patients in the 3% NaCl group were entered into the study over a period ranging from 1.5 to 3 hours (mean = 2.1 ± 0.4 hours) from the time of injury. The time of entry for the lactated Ringer's patients ranged from 2 to 5 hours (mean = 3.5 ± 1.0 hours)($p<0.001$).

Response to Resuscitation Protocol

The cumulative fluid data are summarized in Table V. Significant differences for the cumulative crystalloid replacement were shown during the first 2 hours of the study and subsequent measurements at 3, 8 and 24 hours. At

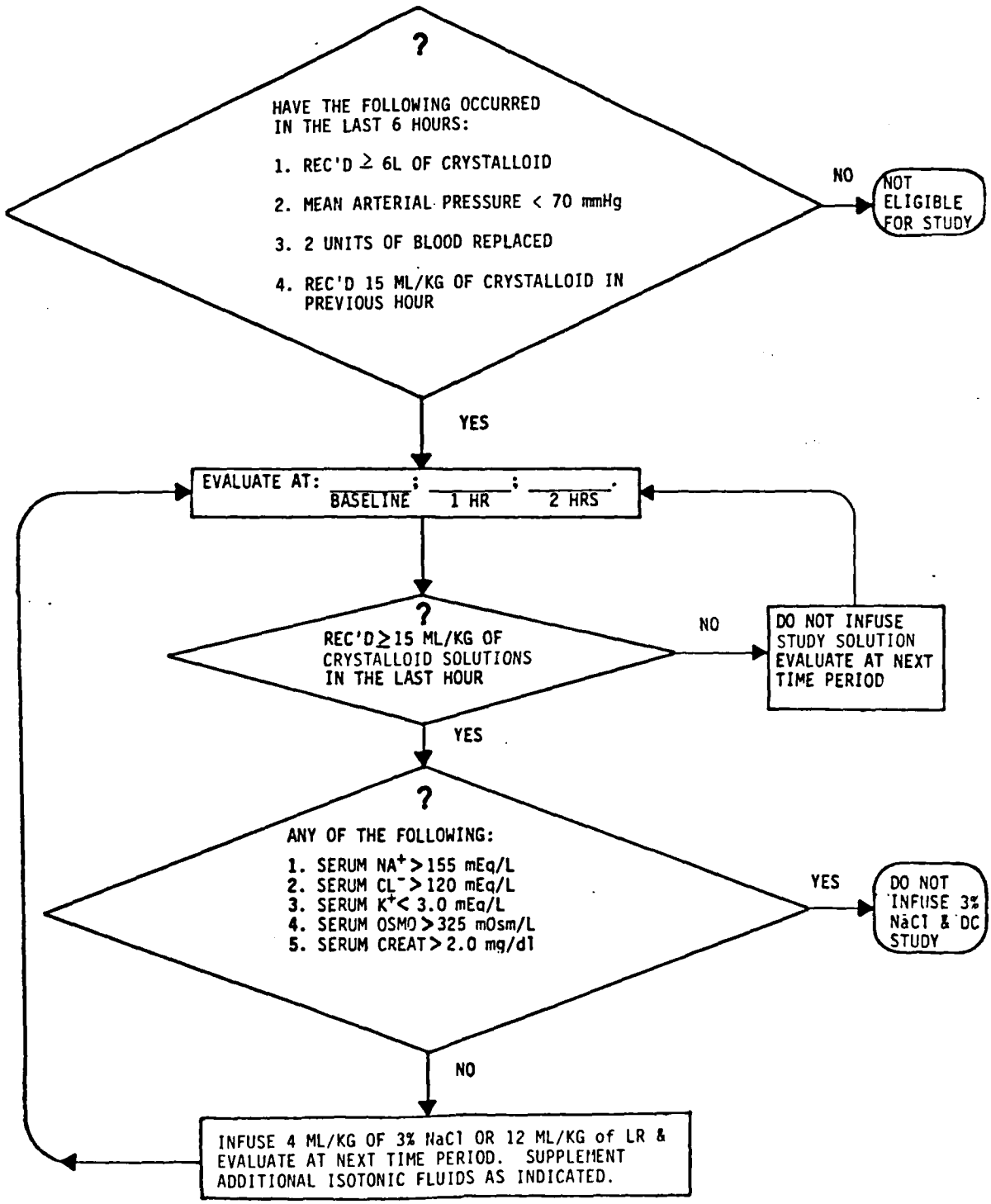

FIGURE 1: ALGORITHM FOR INFUSION OF 3% NaCl OR LR SOLUTION

TABLE I: MECHANISM OF INJURY FOR PATIENTS IN THE 3% NaCl GROUP

PATIENT	AGE/SEX	INJURY	OUTCOME
1	29/M	MCA; open femur fracture; partial, above knee amputation; Type III patellar and tibial plateau fractures; nephrectomy.	Survived
2	29/M	Multiple bilateral stab wounds to chest with hemothorax.	Died; 1 hour
3	26/F	MVA; pelvic, fibular head and ankle fractures; ruptured bladder.	Survived
4	29/M	Depressed frontal skull fracture; multiple stab wounds with bowel perforation, laceration of stomach and kidney.	Survived
5	24/M	MVA; bilateral pulmonary contusions with rib fractures; pelvic fracture, retroperitoneal hematoma, comminuted femur fracture; bilateral upper extremity fractures; splenic rupture; kidney fracture.	Died; day 6
6	20/M	MVA, flail chest; ruptured spleen, large retroperitoneal hematoma, acetabular fracture, fractured tibial shaft and radius.	Survived
7	49/M	Stab wounds to chest, colon, and small bowel enterotomies, hemothorax.	Survived
8	64/M	Stab wounds to chest, left ventricle and abdomen; hemopericardium.	Survived
9	39/M	Stab wound to internal mammary artery, right hemidiaphragm and liver.	Died; day 25
10	39/M	Pelvic fracture with functional hemipelvectomy; transected sigmoid colon; avulsed ileum; ruptured bladder.	Died; day 8

TABLE II: MECHANISM OF INJURY FOR PATIENTS IN THE LACTATED RINGER'S GROUP

PATIENT	AGE/SEX	INJURY	OUTCOME
1	87/F	MVA; multiple rib fractures; pneumothorax; unstable pelvic fracture retroperitoneal hemorrhage.	Died; 2 hours
2	55/M	MVA; unstable pelvic fracture; bimalleolar ankle fracture; humerus fracture; brachial and popliteal artery injuries.	Died; day 74
3	28/M	MVA; pelvic fracture; open femur fracture; open tibia fracture.	Survived
4	19/M	Shotgun blast to right flank; multiple small bowel enterotomies, liver laceration, transection of transverse colon; multiple blast injuries to duodenum, head of pancreas, blow out of stomach and through-and-through splenic injuries.	Survived
5	29/M	Stab wound to epigastrium, with laceration to hepatic vein and left lobe of liver, multiple stab wounds to arm and forearm.	Survived
6	33/M	Multiple stab wounds to neck, head, bilateral chest, arm, and thigh; lacerated pulmonary artery and lacerated liver.	Died; day 87
7	33/M	Multiple gunshot wounds to shoulder, chest, flank, and abdomen; resulting in bilateral hemothoraces, multiple enterotomies; through-and-through wound to liver and axillary artery transection.	Survived
8	21/M	Stab wounds to colon; infrarenal abdominal aorta and infrarenal inferior vena cava.	Survived
9	39/M	MVA; near amputation right foot; open Type III left talus fracture bilateral upper extremity fractures; bilateral rib fractures; transverse lumbar spine fracture; ruptured spleen.	Survived
10	26/M	Multiple gunshot wounds to axilla, arm, chest, abdomen, and thigh; resulting in hemothorax; multiple jejunoenterotomies; nephrectomy; femur fracture; popliteal artery transection.	Survived

TABLE III: CONDITION OF PATIENTS AT TIME OF ENTRY INTO STUDY

	3% NaCl		Lactated Ringer's
	Mean ± SD		Mean ± SD
AGE	36 ± 13		36 ± 21
GLASGOW COMA SCORE	14 ± 1		11 ± 6
TIME BEFORE ENTRY (HOURS)	2.1 ± 0.4		3.5 ± 1.0
INJURY SEVERITY SCORE	34 ± 10		33 ± 8
SYSTOLIC BP (mmHg)	98 ± 41		105 ± 29
HR (beats/min)	107 ± 39		114 ± 13
P_aO_2/F_iO_2 (mmHg) [1]	240 ± 131	*	380 ± 135
P_aCO_2 (mmHg)	39 ± 4		36 ± 5
pH	7.26 ± 0.08		7.22 ± 0.13
HCO_3 (mEq/L)	18 ± 3		17 ± 5
SODIUM (mEq/L)	144 ± 3		145 ± 5
POTASSIUM (mEq/L)	3.8 ± 0.5		3.7 ± 0.3
CHLORIDE (mEq/L)	111 ± 7		109 ± 4
BUN (mEq/L)	11 ± 4		11 ± 4
CREATININE (mg/dl)	1.0 ± 0.2		0.9 ± 0.3
BILIRUBIN (mg/dl)	0.8 ± 0.4		0.8 ± 0.3
OSMOLALITY (mOsm/L)	308 ± 20		303 ± 10
HEMATOCRIT (%)	25.5 ± 7.6		22.7 ± 8.8
PLATELET COUNT (cells/mcl)	231,000 ± 17,000	*	149,000 ± 77,000
BLOOD REPLACEMENT	23 ± 18		24 ± 17
CUMULATIVE SODIUM ADMINISTERED (mEq/kg)	14 ± 3		17 ± 4

*Difference between groups ($p<0.03$).

1) P_aO_2/F_iO_2 = Ratio of partial pressure of oxygen in systemic arterial blood to fractional inspired oxygen concentration (Normal = approximately 450).

TABLE IV: FLUID STATUS AT TIME OF ENTRY INTO STUDY

	3% NaCl	Lactated Ringer's
	Mean ± SD	Mean ± SD
CRYSTALLOID Administered (ml/kg)	102 ± 20	120 ± 30
BLOOD REPLACEMENT (ml/kg)	23 ± 18	24 ± 17
SODIUM Administered (mEq/kg)	14 ± 3	17 ± 4
URINE OUTPUT (ml/kg)	3.4 ± 2.3	6.9 ± 6.6

TABLE V: CUMULATIVE 24-HOUR FLUID DATA

	1 Hour	2 Hours	3 Hours	4 Hours	8 Hours	24 Hours
Crystalloid Replacement (ml/kg)						
3% NaCl	20±10	39±17	57±23	73±32	103±52	189±139
Isotonic	32±16	69±35	94±46	115±73	187±83	311±107
P	0.05	0.03	0.05	0.09	0.02	0.05
Fluid Balance (ml/kg)						
3% NaCl	17±11	30±21	44±28	58±38	81±51	148±141
Isotonic	28±15	60±37	89±45	109±56	203±107	304±119
P	0.12	0.04	0.02	0.04	0.008	0.02
Sodium Administered (mEq/kg)						
3% NaCl	4.6±1.5	8.5±2.9	11.7±4.3	14.0±5.8	18.1±8.1	29.1±21.5
Isotonic	4.8±2.8	9.5±4.4	12.0±4.9	16.4±7.5	26.0±10.2	40.4±15.7
P	NS	NS	NS	NS	NS	NS
Blood Replacement (ml/kg)						
3% NaCl	15±20	19±25	24±27	31±36	41±48	65±91
Isotonic	14±11	26±22	26±22	30±23	41±26	60±35
P	NS	NS	NS	NS	NS	NS
Urine Output (ml/kg)						
3% NaCl	3.9±2.6	8.8±6.9	13.3±7.8	15.0±8.8	21.6±10.4	41.3±20.0
Isotonic	1.9±2.1	3.0±2.7	4.8±2.9	6.4±3.6	10.2±3.8	30.6±11.6
P	0.08	0.02	0.007	0.02	0.007	NS

the end of two hours, the volume of fluid required by the 3% NaCl group was 39 ± 17 $ml \cdot kg^{-1}$. This was significantly less ($p<0.03$) than the 69 ± 35 $ml \cdot kg^{-1}$ of fluid required by the lactated Ringer's group to maintain hemodynamic stability. At 8 hours, the cumulative volume of crystalloid administered was 103 ± 52 ($ml \cdot kg^{-1}$) for the 3% NaCl group versus 187 ± 83 ($p<0.04$) for the lactated Ringer's group. By 24 hours, the 3% NaCl group had received 189 ± 139 ml/kg of crystalloid versus 311 ± 107 ($p=0.05$) in the lactated Ringer's group.

The cumulative 24 hour fluid balance was determined by calculating the difference between the cumulative crystalloid and urine output. The cumulative fluid balance was significantly greater in the lactated Ringer's group at 2 hours and throughout the remaining first 24 hours.

Figure 2 shows individual volumes (in milliliters) of 3% NaCl administered for the three hour study period. The volume of 3% NaCl administered at the end of 1 hour was 4.0 ± 0.0 $ml \cdot kg^{-1}$. Two patients had the 3% NaCl infusion stopped at this time due to serum sodium concentrations above 155 mEq/L. The infusion was stopped in a third patient who no longer required 15 $ml \cdot kg^{-1} \cdot hr^{-1}$ of fluid. A fourth patient in the 3% NaCl group died during the first hour. All of the patients in the 3% NaCl group received supplemental isotonic solutions throughout the 3 hour study period. Only one lactated Ringer's patient was eliminated at the end of one hour, as he no longer required 15 $ml \cdot kg^{-1} \cdot hr^{-1}$ of fluid.

At the end of two hours, five patients in the 3% NaCl group had the infusion stopped as they no longer required 15 $ml \cdot kg^{-1} \cdot hr^{-1}$ of fluid. A sixth patient had the infusion stopped for a serum sodium concentration above 155 mEq/L, measured at the end of the first hour and reported one hour later. This resulted in the nine patients who were alive at the end of two hours receiving an average of 7.0 ± 1.6 $ml \cdot kg^{-1}$ of the 3% NaCl solution. Three of the patients received the 3% NaCl solution for the full three hour period. This resulted in an average volume of 8.3 ± 3.1 $ml \cdot kg^{-1}$ of 3% NaCl being administered over the 3 hour study period. In the lactated Ringer's group, one patient died at the end of two hours. The remaining lactated Ringer's patients continued to require at least 15 $ml \cdot kg^{-1} \cdot hr$ of fluid at the end of the second and third hour evaluation periods.

During the course of the first three hours of the study, each group received equivalent amounts of blood and sodium. This continued throughout the 24 hour evaluation period.

In conjunction with decreased fluid requirements, the cumulative urine output was 8.8 ± 7.0 $ml \cdot kg^{-1}$ at the end of two hours in the 3% NaCl group versus 3.0 ± 2.3 $ml \cdot kg^{-1}$ in the lactated Ringer's group ($p<0.02$). Urine output remained significantly improved in the 3% NaCl for up to 8 hours.

Systolic blood pressures and heart rates were comparable throughout the 24 hour study period (Table VI).

All patients were mechanically ventilated on 100% oxygen at the time of entry into the study. The P_aO_2/F_iO_2 ratios remained stable throughout the 24 hour study period in the 3% NaCl group. The P_aO_2/F_iO_2 ratios in the lactated Ringer's group, which were better at the time of entry, deterioriated

throughout the 24 hour period. At the end of 24 hours, the mean P_aO_2/F_iO_2 ratio for the 3% NaCl group was 256 ± 108 versus 197 ± 94 ($p<0.05$) in the lactated Ringer's. However, the difference between the baseline (380 ± 135) and 24 hour values (197 ± 94) for the patients in the lactated Ringer's group was significant ($p<0.003$). The baseline and 1 hour pH measurements were equivalent. At 4 hours, the pH in the 3% NaCl group had increased to 7.33 ± 0.07 versus 7.24 ± 0.07 ($p<0.02$) in the lactated Ringer's group. At 8 hours, the mean pH for the 3% NaCl group had risen to 7.36 ± 0.07 versus 7.27 ± 0.08 ($p<0.03$) in the lactated Ringer's group. By 24 hours, the values for each group were similar (Table VI).

Table VII sumarizes the 24 hour laboratory measurements. Serum sodium concentrations were found to be significantly increased in the 3% NaCl group at 1 hour -- 152 ± 6 versus 146 ± 2 ($p<0.02$). There were no further differences at 4,8, and 24 hours. The maximum serum sodium concentration was 162 mEq/L in a patient who received 400 ml of 3% NaCl. In addition, he had received 10 ampules of sodium bicarbonate during the second hour of the study.

Serum chloride concentrations were elevated to 117 ± 6 at 1 hour in the 3% NaCl group versus 110 ± 5 ($p<0.01$) in the lactated Ringer's group. The values were no longer different at 4,8, and 24 hours. The maximum serum chloride was 130 mEq/L in the same patient mentioned above.

Serum osmolality in the 3% NaCl group was elevated to 313 ± 11 at 1 hour versus 299 ± 8 ($p<0.02$) in the lactated Ringer's group. The 4 hour serum osmolality remained elevated at 311 ± 13 versus 302 ± 6 ($p<0.04$). These differences did not persist at 8 and 24 hours. The maximum serum osmolality was 370 mOsm/L in the same patient with the highest serum sodium and chloride levels.

The 3% NaCl solution was infused into a central vein in 3 patients and into a peripheral vein in 7 patients. There was no evidence of irritation or venous thrombosis.

Measurements of additional cardiorespiratory and renal function parameters were attempted. However, central venous and pulmonary artery catheters were not routinely available during the early phase of the patient resuscitation. Subsequently, we were unable to assess the response of oxygen consumption, pulmonary artery pressure and cardiac index to the 3% NaCl infusion. Urine electrolytes were obtainable in a few patients from each group. Accurate measurements were usually not logistically possible due to the emergent conditions in the operating room, numerous diagnostic procedures, dye injections and bladder irrigations. Twenty-four hour creatinine clearances were obtained in 5 of the 3% NaCl and 4 of the lactated Ringer's patients. The average values were within normal limits for each group -- 98 ± 48 $ml \cdot min \cdot^{-1}$ in the 3% Nacl group versus 71 ± 26 in the lactated Ringer's group ($p<0.05$).

Additional evaluations of fluid status, performed for up to 7 days after entry into the study did not show any differences between the two groups. Similar follow-up of pulmonary function did not show any differences for the first 7 days, nor at 14 and 30 days after entry into the study.

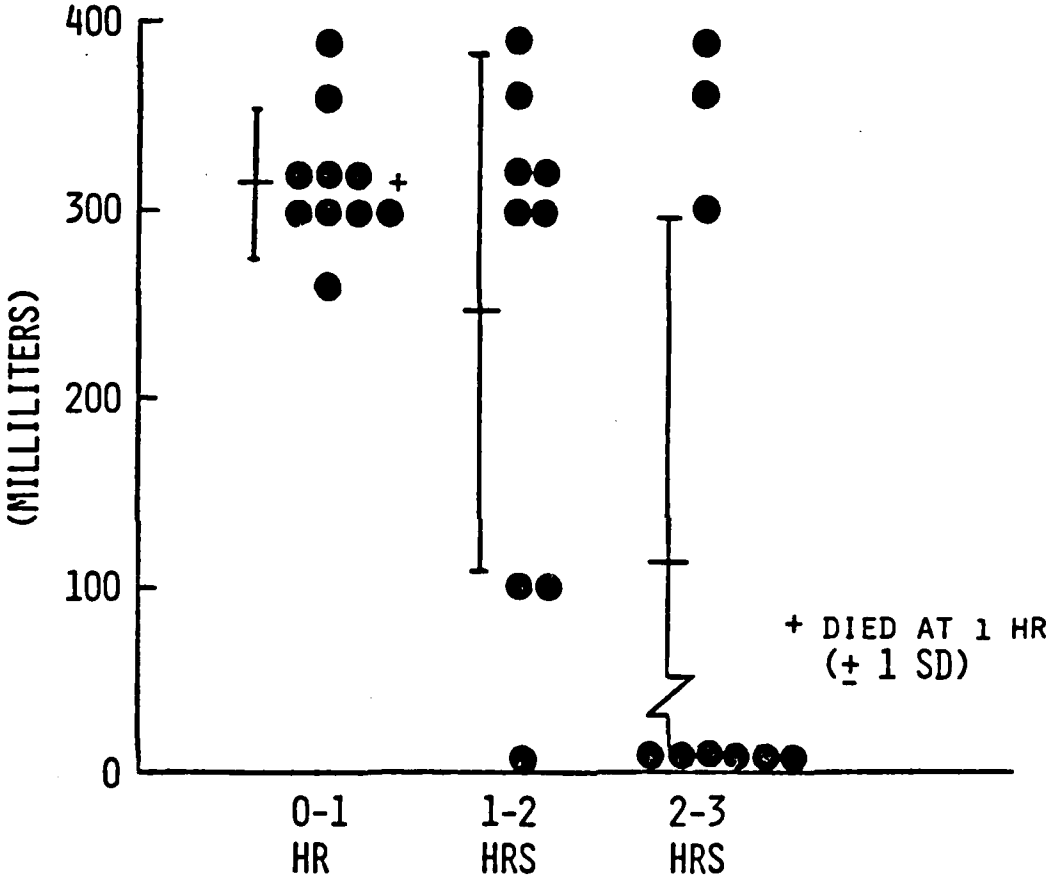

FIGURE 2: VOLUME OF 3% SODIUM CHLORIDE SOLUTION ADMINISTERED DURING THE 3 HOUR INFUSION PERIOD.

TABLE VI: 24-HOUR CARDIORESPIRATORY DATA

	1 Hour	2 Hours	3 Hours	4 Hours	8 Hours	24 Hours
Systolic Blood Pressure (mmHg)						
3% NaCl	117±23	116±29	119±30	118±29	123±23	129±17
n	9	9	9	9	9	9
Isotonic	111±15	117±18	118±21	124±21	125±26	144±22
n	10	10	9	9	9	9
Heart Rate (Beat/min)						
3% NaCl	106±21	114±24	108±12	116±20	111±28	108±16
n	9	9	9	9	9	9
Isotonic	115±12	112±18	128±17	125±17	125±19	125±11
n	10	10	9	9	9	9
P_aO_2/F_iO_2 Index						
3% NaCl	276±120	269±136	---	250±116	245±156	256±108
n	9	8		9	9	9
Isotonic	301±184	227±126	---	310±123	234±122	197±94
n	7	6		7	9	8
P_aCO_2						
3% NaCl	38±7	39±5	---	38±7	41±10	40±4
n	9	8		9	9	9
Isotonic	39±9	38±10	---	39±5	41±4	37±9
n	7	6		7	9	8
pH						
3% NaCl	7.27±0.08	7.24±0.12	---	7.33±0.07*	7.36±0.07*	7.37±0.07
n	9	8		9	9	9
Isotonic	7.27±0.07	7.26±0.08	---	7.24±0.07	7.27±0.08	7.39±0.09
n	7	6		7	9	9

* $p<0.02$ for unpaired t-test

** $p<0.009$ for difference between baseline and 8 hour measurement by paired t-test for isotonic patients

\+ $p<0.003$ for difference between baseline and 24 hour measurement by paired t-test for isotonic patients

TABLE VII: 24 HOUR SERUM ELECTROLYTES AND HEMATOCRITS

	1 Hour	4 Hours	8 Hours	24 Hours
Sodium (meq/l)				
3% NaCl	152±6	151±5	150±7	148±7
n	9	9	9	9
Isotonic	146±2	146±5	145±5	144±4
n	10	8	9	9
Potassium (meq/l)				
3% NaCl	3.8±0.9	3.9±0.8	4.2±0.4	4.0±0.5
n	9	9	9	9
Isotonic	4.2±0.4	4.5±0.9	4.8±0.7	4.1±0.5
n	10	8	9	9
Chloride (meq/l)				
3% NaCl	117±6	117±6	116±6	113±6
n	9	9	9	9
Isotonic	110±5	113±2	113±3	111±6
n	10	8	9	9
Osmolality (mg/dl)				
3% NaCl	319±24	313±11	311±13	303±12
n	9	9	9	9
Isotonic	299±8	302±6	300±5	296±6
n	10	8	9	9
BUN (mg/dl)				
3% NaCl	11±3	10±3	11±3	13±3
n	9	9	9	9
Isotonic	10±2	10±2	10±3	13±3
n	9	8	9	9
Glucose (mg/dl)				
3% NaCl	179±62	163±42	164±54	128±30
n	9	9	9	9
Isotonic	207±107	2110±115	166±88	145±63
n	10	8	9	9
Bicarbonate (meq/l)				
3% NaCl	22±8	21±4	22±3	24±2
n	9	9	9	9
Isotonic	17±14	19±3	21±2	23±4
n	10	8	9	9
Creatinine (mg/dl)				
3% NaCl	0.9±0.1	0.9±0.1	0.9±0.1	1.2±0.6
n	7	8	7	9
Isotonic	0.9±0.1	0.9±0.1	0.9±0.1	1.0±0.2
n	7	5	7	9
Hematocrit (%)				
3% NaCl	29±5	32±4	33±5	28±5
n	9	9	9	9
Isotonic	25±8	27±8	29±8	33±4
n	10	9	9	9

Post-Resuscitation Clinical Course

After operation, all patients required mechanical ventilation and were admitted to the intensive care unit. In the 3% NaCl group, two patients were extubated by the end of the first 24 hours. Two more patients were extubated at 48 hours. One of these patients required re-intubation 5 days later. One patient died on day 6, a second patient died on day 8, and a third died 25 days after entry into the study. In the lactated Ringer's group, the first patient was extubated at 3 days. One patient died at 49 days, a second patient died 83 days after entry into the study. The 30 day mortality of 40% in the 3% NaCl group was not significantly different from the 10% mortality in the lactated Ringer's group. The final overall mortality in the lactated Ringer's group was 40%.

Details of the clinical outcomes are shown in Table VIII. The data for days of mechanical ventilation, days in the intensive care unit and days of hospitalization include the values for the non-survivors. Despite the intitial stability of pulmonary function in the 3% NaCl group, seven patients developed respiratory failure, along with nine patients in the lactated Ringer's group. Only three patients in the 3% NaCl group remained free from postoperative complications of organ failure. All of the lactated Ringer's patients developed failure of one or more organs.

Conclusion

In summary, the short term results in this small number of patients were far better than we had anticipated, allowing us to terminate the study one year earlier than we predicted. In 20 patients, we found that the 3% NaCl solution achieved excellent resuscitation with less volume than was required by the lactated Ringer's group. This was achieved within two hours after entry into the study. All of the patients were seriously injured and these injuries were comparable, based on the injury severity scores and blood loss at time of entry and over the subsequent 24 hour study period. The 3% NaCl solution provided a more rapid correction of metabolic acidosis and improved urine output while maintaining cardiovascular and pulmonary stability throughout the study. The marked deterioration in the P_aO_2/F_iO_2 ratio in the lactated Ringer's group lends further support to the advantages of reducing water load by resuscitation with hypertonic solutions. The outcomes, in terms of development of organ failure were similar for the two groups. Despite the encouraging findings in the first 24 hours of the study, seven patients in the 3% NaCl group and ten of the patients in the lactated Ringer's group developed failure of one or more organs. Lastly, the early benefits of the 3% NaCl solution were not associated with any evidence of improved long-term survival.

Recommendations

The results of this first trial in a group of severely injured patients are promising. We have documented the safety and short-term efficacy of a 3% NaCl solution in moderate volumes. This should prompt double-blinded trials of solutions with higher sodium concentrations earlier in the course of resuscitation where they are expected to be of the most benefit to the injured soldier or civilian.

TABLE VIII: OUTCOME

	3% NaCl	Lactated Ringer's
LENGTH OF OPERATION (Hours)	3.6 ± 2.0	5.7 ± 4.0
OVERALL SURVIVAL	6/10	7/10
DAYS OF MECHANICAL VENTILATION	14 ± 20	29 ± 26
DAYS IN INTENSIVE CARE UNIT	18 ± 27	38 ± 30
DAYS OF HOSPITALIZATION	28 ± 36	49 ± 38
RESPIRATORY FAILURE	7/10	9/10
CARDIAC FAILURE	1/10	0/10
HEPATIC FAILURE	4/10	4/10
RENAL FAILURE	2/10	1/10
GASTROINTESTINAL FAILURE	0/10	0/10
COAGULATION FAILURE	1/10	2/10
NO ORGAN FAILURE	3/10	0/10
SINGLE ORGAN FAILURE	2/10	5/10
TWO OR MORE ORGAN FAILURES	5/10	5/10

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RESUSCITATION OF SEVERELY INJURED PATIENTS WITH A 3% NaCl SOLUTION

James W. Holcroft, M.D., Mary J. Vassar, R.N., F. William Blaisdell, M.D.
University of California, Davis, Medical Center, Sacramento, California

Achieving adequate resuscitation of severely injured hypovolemic patients by emergency medical technicians in the field is close to impossible because only small amounts of fluid can be delivered through percutaneously-placed peripheral venous catheters. A fluid that could resuscitate with small volumes would solve this problem. Twenty patients with severe injuries (average ISS of 33) were entered into a prospective trial. All patients had been injured within the preceding 6 hours; all had received at least 6 liters of fluid for initial resuscitation. Ten patients of one attending surgeon received 3% NaCl, 4 ml/kg/hr, for no more than 3 hours as their primary asanguinous fluid resuscitation, with isotonic solutions given in addition as needed. Ten matched patients of a second attending, studied during the same time period and treated by the same team, received only isotonic solutions.

	Baseline	2 Hours	4 Hours	8 Hours	24 Hours
Blood pressure					
3% NaCl	100±39	116±29	118±29	123±23	129±17
Isotonic	112±25	117±18	124±21	125±26	144±22
pH					
3% NaCl	7.27±0.08	7.24±0.12	7.33±0.07	7.36±0.07	7.37±0.07
Isotonic	7.26±0.09	7.26±0.08	7.24±0.07	7.27±0.08	7.39±0.09
		NS	P=0.02	p=0.03	NS
Urine output (ml/kg)					
3% NaCl	3.4±2.3	8.8±6.9	15.0±8.8	21.6±10.4	41.3±20.0
Isotonic	6.9±6.6	3.0±2.7	6.4±3.6	10.2±3.8	30.6±11.6
		p=0.01	NS	NS	.NS
Fluid balance (ml/kg)					
3%	99±20	30±21	58±38	81±57	148±141
Isotonic	113±27	60±37	109±56	203±107	304±119
		p=0.03	p=0.06	p=0.01	p=0.02

Means ± 1 SD. Values over 24 hours showed no significant difference between the treatments by repeated measures ANOVA. Compared with control patients, however, the pH in the 3% NaCl group was improved by 4 hours; cummulative urine output was greater during the time that the 3% NaCl was being infused; and fluid balance was better for up to 24 hours (by Student's T-test on logarithmically transformed values). Serum sodiums were 152±6 mEq/l at 1 hour; osmolalities were 319±24 mOsm/kg. The solution caused no phlebitis, and no complications developed with its use. Conclusion: 3% NaCl achieved resuscitation and maintained cardiovascular stability with less fluid than that needed with isotonic solutions. Hypertonic solutions may be an answer to the problem of achieving field resuscitation of severely injured patients with small fluid volumes.

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